

Pharmacokinetics Studies of Levofloxacin in Children Exposed to Multidrug-Resistant Tuberculosis — United States Affiliated Pacific Islands, 2008–2011

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Multidrug-resistant TB (MDR TB)

- TB that is resistant to at least isoniazid & rifampin (most effective medications)
- Public health emergency
 - Case-fatality rate is higher
 - Longer duration of treatment
 - More costly to treat
 - Adverse effects of treatment more common

MDR TB in the U.S. Affiliated Pacific Islands (USAPI)

- Federated States of Micronesia (FSM) and the Republic of the Marshall Islands (RMI) are 2 of the 6 USAPI with recent investigations into MDR TB emergence
- MDR TB investigation in Chuuk, FSM, in June 2008 by CDC, WHO, & Secretariat of the Pacific Community (SPC)
- MDR TB investigation in the RMI in October 2009 by CDC & WHO

Investigations and Studies of MDR TB in USAPI

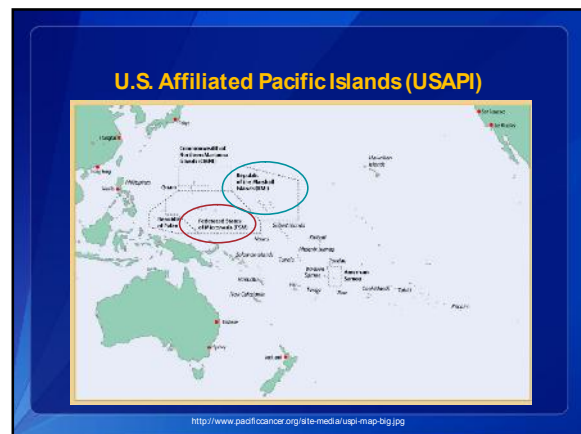
- 1) Background on the USAPI
- 2) Epidemiology of TB in the region
- 3) Review of MDR TB outbreaks in the region & outbreak response, including capacity-building for MDR TB
- 4) Pharmacokinetics of levofloxacin in children



U.S. Affiliated Pacific Islands (USAPI)



<http://www.pacificcancer.org/site-media/upi-map-big.jpg>



U.S. Affiliated Pacific Islands (USAPI)

❑ Six jurisdictions affiliated with the United States

Current political relationship	Country
Trust territory	American Samoa
	Guam
Commonwealth	Commonwealth of the Northern Mariana Islands
Freely Associated State under Compact of Free Association	Federated States of Micronesia (FSM)
	Republic of the Marshall Islands (RMI)
	Republic of Palau

- ### Compact of Free Association
- ❑ First approved in 1986, renewed in 2003 through 2023 for FSM & RMI
 - ❑ Guarantees financial assistance through the Office of Insular Affairs
 - ❑ Grants the United States full defense authority & responsibilities (i.e., strategic military benefits)
 - ❑ Includes economic provisions, broad migration rights (i.e., right to reside & work in United States)

Economy & Geography — FSM & RMI

	FSM	RMI
Economy	•Economic assistance provides >50% of its GDP	•Economic assistance provides >70% of its GDP
Geography	•About 2,500 miles from Hawaii •Over 600 islands •Land area: 270 square miles •Spread over 1,000,000 square miles •Estimated population: 107,434	•About 2,136 miles from Hawaii •Five islands, 29 atolls •Land area: 70 square miles •Spread over 750,000 square miles •Estimated population: 51,484

May 2010

- ❑ Regional health emergency declared for USAPI
- ❑ Issued by Pacific Island Health Officers Association
- ❑ Epidemic of non-communicable diseases, including diabetes

Regional Health Emergency Declared
Due to Epidemic of Non-Communicable Diseases
In the United States Affiliated Pacific Islands (USAPI)

The Pacific Island Health Officers Association (PIHOA) has declared a regional health emergency in the United States Affiliated Pacific Islands (USAPI) due to the epidemic of non-communicable diseases (NCDs), specifically diabetes.

The emergency was declared on May 10, 2010, following a meeting of the PIHOA members. The meeting was held in the Federated States of Micronesia (FSM) and was attended by representatives from the USAPI region, including the United States, the Federated States of Micronesia (FSM), the Republic of the Marshall Islands (RMI), and the Republic of Palau.

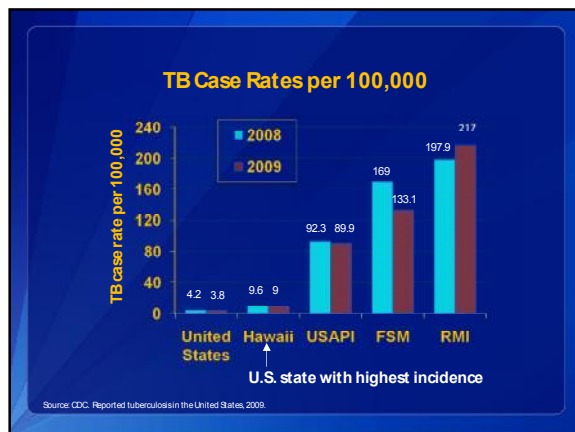
The emergency was declared because of the high prevalence of NCDs in the USAPI region. According to the PIHOA, the prevalence of NCDs in the USAPI region is significantly higher than in other parts of the Pacific region. This is due to a variety of factors, including changes in diet, lifestyle, and aging populations.

The emergency was declared to draw attention to the problem and to encourage action to be taken to address it. The PIHOA is calling on the USAPI region to take action to reduce the burden of NCDs. This includes improving diet and lifestyle, increasing physical activity, and improving access to health care.

The PIHOA is also calling on the United States to provide support to the USAPI region in addressing the epidemic of NCDs. This includes providing financial and technical assistance, and supporting the development of health systems in the USAPI region.

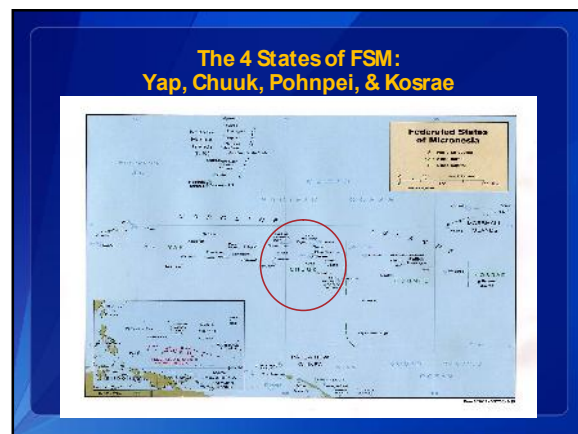
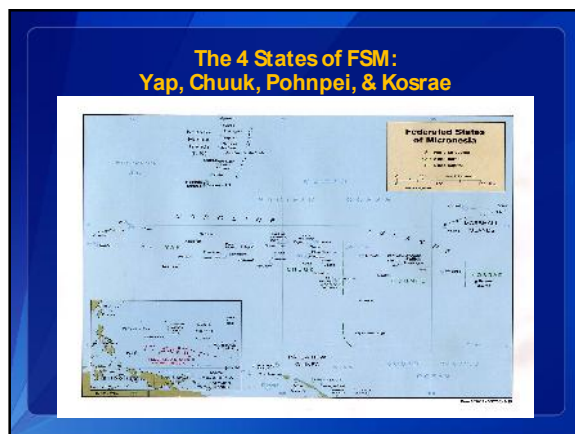
The PIHOA is committed to working with the USAPI region to address the epidemic of NCDs. The PIHOA will continue to monitor the situation and will report back to the USAPI region on the progress of the emergency response.

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MDR TB Outbreaks
CHUUK STATE—FSM*

*Investigation & post-outbreak response led by Dr. Sapna Bamrah, CDC, DTBE



- ### MDR TB in Chuuk, FSM
- ❑ During April 2007–June 2008, four cases of laboratory-confirmed MDR TB were reported in Chuuk
 - ❑ Three (75%) of 4 patients had died
 - ❑ 2-year-old child and mother with MDR TB → evidence of recent transmission
 - ❑ No 2nd line medications available as of June 2008

Summary Results of Chuuk Investigation, July 2008

- ❑ Two distinct, simultaneous MDR TB outbreaks
 - 5 confirmed MDR TB cases
 - 7 new suspected MDR TB cases
 - 205 identified contacts
 - At least 124 (60%) with latent TB infection (LTBI)

Weno Island, Chuuk



Photo courtesy of Dr. Sagna Bamrah (CDC, DTEE)

Emergence of MDR TB in Chuuk State

- ❑ **Strain A resistant to INH, RIF, PZA, EMB, & streptomycin**
 - Primary resistance
 - Likely imported
- ❑ **Strain B resistant to INH, RIF, & ethionamide**
 - Secondary resistance
 - Circulating strain resistant to INH & ethionamide acquired RIF resistance

Post-investigation Activities

Priority	Action
Complete evaluation of contacts	Hired & trained contact tracing staff; assisted by USNS Mercy in finding active cases among contacts
Isolate & treat MDR TB cases	Acquired 2 nd line drugs; consultation with FJ Curry Center & MDR TB experts; onsite training of physicians; built isolation ward at hospital
Prevent future acquired MDR TB cases through 100% DOT	Hired & trained additional DOT workers to ensure DOT for all TB cases
Avert future MDR TB among contacts with presumed drug-resistant infection	LTBI treatment by DOT with fluoroquinolone + ethionamide (strain A) or ethambutol (strain B)
Transport patients, specimens	Purchased 4-wheel drive vehicles, gas

Chuuk Experience

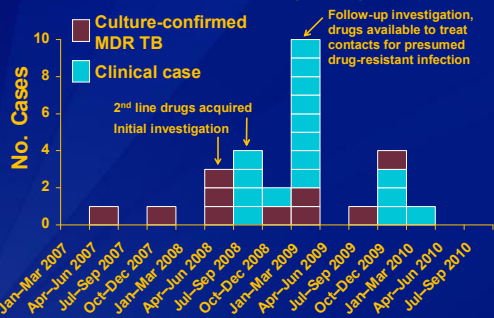
- ❑ 10 contacts developed TB disease while awaiting LTBI treatment
- ❑ 6 contacts not on LTBI treatment developed TB disease
- ❑ No contacts treated for LTBI developed TB disease

LTBI treatment initiation & completion



*Data are courtesy of Dr. Sagna Bamrah, CDC, DTEE

MDR TB Cases— Chuuk, 2007–2010* (n=27)



* as of November 9, 2010

MDR TB Outbreaks

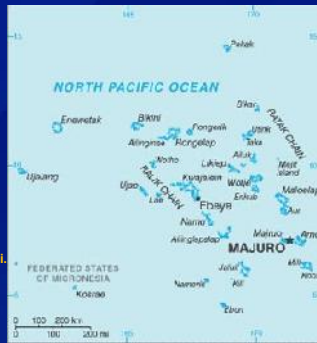
MAJURO & EBeye — RMI

Two Major Population Centers in the RMI: Majuro & Ebeye

- 70% of population resides on these two islands

- **Majuro** (capital) in the Majuro Atoll
 - About half of population resides on Majuro

- **Ebeye** in the Kwajalein Atoll
 - Pop. density 72,000 / sq. mi.
 - Many internally displaced



Ebeye Island, Kwajalein Atoll, RMI



Total land area: 0.14 square miles
Estimated population: 10,000 persons
Population density: 72,000 persons/square mile

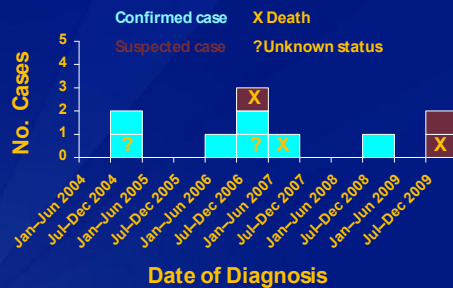
MDR TB in the RMI, 2004–2009

- ❑ Six cases of MDR TB reported through passive standard surveillance
- ❑ Cases diagnosed in both major population centers (Majuro & Ebeye)
- ❑ Initial contact tracings were limited but suggested substantial transmission around most recently diagnosed case
- ❑ Limited resources for contact investigation & limited access to 2nd line medications

Summary of Results from RMI Investigation, October–November 2009

- ❑ No known epidemiologic links between Ebeye (n=6) & Majuro cases (n=4)
- ❑ All cases epidemiologically linked on Majuro
 - Three cases associated with household transmission
 - One case in HCW associated with nosocomial transmission
- ❑ No clear epidemiologic links among cases on Ebeye
 - Transmission site could not be determined
 - Three patients had received previous TB treatment but DOT was not effectively documented (incomplete self-administered treatment → acquired multidrug-resistance?)

Confirmed & Suspected MDR TB cases — RMI, 2004–2009 (n=10)



Contact Investigation Summary — RMI, as of October 2010

Category	Number	Percent of previous row
Contacts identified	284	—
Contacts evaluated with TST	172	61%
Contacts with pos TST ^a	65	37%
Contacts with LTBI who initiated treatment for drug-resistant infection ^b	51	78%
Contacts who remain on treatment for drug-resistant infection	47	92%

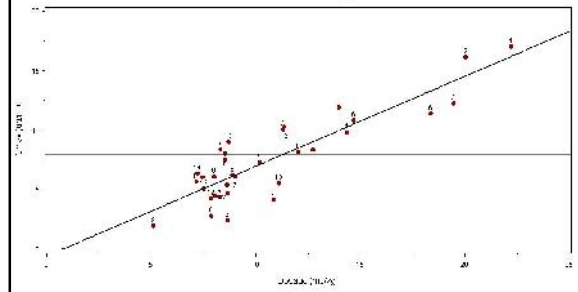
^aNo additional MDR TB cases were identified among contacts.

^bMDR TB expert panel recommended 1-year regimen of ethambutol and a fluoroquinolone.

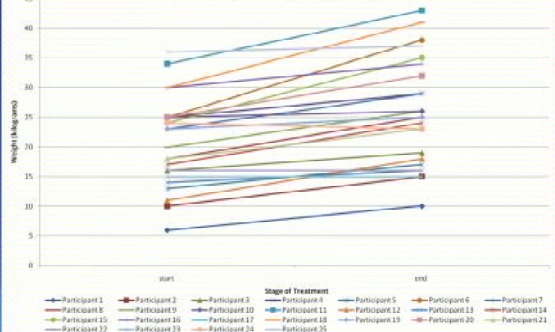
PK Study During Treatment of MDR LTBI, Contacts in Chuuk

- ❑ **Adults: Moxifloxacin or Moxifloxacin + EMB**
- ❑ **Children: Levofloxacin or Levofloxacin + EMB**
 - 15–20 mg/kg for children 5 years old or younger
 - 10 mg/kg for children older than age 5 years
 - Target Cmax 8–10 µg/ml
- ❑ All treatment DOT daily for 1 year
- ❑ PK study
 - Doses observed at hospital
 - Blood collection at 1, 2, 5 hours after dose
 - Drug concentrations measured by Charles Peliccioli

Cmax vs. Dosage



Weight changes among study participants



Acknowledgments

- Chuuk State Governor's Office
- Chuuk State Dept of Health Services
- Chuuk State TB Program
- FSM National TB Program
- RMI Ministry of Health
- RMI National TB Program
- Village Chiefs, other community leaders
- Centers for Disease Control and Prevention
- U.S. Department of Interior
- WPRO, World Health Organization
- Secretariat for the Pacific Community
- DLS & MDL contract labs
- CNMI Public Health Department
- Pacific Islands Health Officers Association
- Pacific Islands TB Controllers Association

